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Mixed Carboxylic Anhydrides in the Grignard Reaction.

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MIXED CARBOXYLIC ANHYDRIDES IN THE GRIGNARD REACTION

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ABSTRACT

The purpose of this work was to study the reactions of mixed carboxylic anhydrides with Grignard reagents. The reactions were carried out in most cases using equimolar portions of anhydride and Grignard reagent, in ether solution, and at approximately -78° C. to increase the yields of the two carbonyl compounds possible from each mixed anhydride. The relative proportions and absolute quantities of the carbonyl compounds were determined by gas chromatography and distillation. In some reactions, in addition to the carbonyl compounds, small amounts of alcohols were formed, by further reaction of the Grignard reagents at the expense of the carbonyl products. Whenever possible, the proportions and quantities of these alcohols were determined. Attempts were made to correlate the relative reactivities of the acyl groups of the anhydrides, as revealed by the ratios of their reaction products, with the structures of those groups and of the Grignard reagents used.

The reactions of six acetic higher-carboxylic anhydrides with phenylmagnesium bromide were studied: acetic butyric, acetic valeric, acetic caproic, acetic isobutyric, acetic isovaleric, and acetic α-methylbutyric anhydrides. The lower molecular weight ketone always predominated. The proportion of the higher ketone was nearly the

same for the first three (straight-chain) anhydrides, but this proportion decreased for the last three (branched-chain). The reaction of acetic butyric anhydride in tetrahydrofuran showed an increase in the total yield, and a slight increase in the proportion of higher molecular weight ketone. When acetic butyric anhydride was allowed to react with n-propylmagnesium bromide, the ratio of the lower to the higher ketone decreased significantly. The results of these reactions suggested that steric factors were the major controlling influence on the course of the reaction.

A study was made of the reactions of mixtures of acetic and butyric anhydrides, and acetic and valeric anhydrides, with phenylmagnesium bromide. In contrast to their behavior in Friedel-Crafts reactions, the results were similar to the results of the reactions of the corresponding mixed anhydrides.

The major interest of this work involved the reactions of formic acetic anhydride with Grignard reagents. These reactions yielded aldehydes, predominantly; in addition, a measurable amount of ketone usually was formed. This reaction provides a new aldehyde synthesis. Yields of aldehyde ranged from 8 per cent, using propylmagnesium bromide, to 40 per cent, with phenylmagnesium bromide.

Aromatic Grignard reagents allowed to react with formic acetic anhydride included: phenylmagnesium bromide, in both ether and tetrahydrofuran; m-chlorophenylmagnesium bromide; and o-, m-, and p-tolylmagnesium bromides. The aldehyde product nearly always pre-

dominated greatly over the ketone product; an exception was the reaction with phenylmagnesium bromide in tetrahydrofuran, in which there was only a slight predominance of aldehyde over ketone. Of these aromatic Grignard reagents, m-chlorophenylmagnesium bromide gave the lowest aldehyde yield, followed by o-tolylmagnesium bromide. The other three gave approximately the same yields of aldehyde.

Aliphatic Grignard reagents permitted to react with formic acetic achydride were: ethyl-, n-propyl-, n-butyl-, and isobutylmagnesium bromides, and butylmagnesium chloride. Secondary and tertiary alcohols were produced in these reactions, in addition to the aldehydes and ketones. When the ratio of the total reaction products from the formic part of the anhydride to the total products from the acetic part was considered, it was found to be nearly the same for all of the reactions of the straight-chain Grignard reagents, but it was greater for the reactions of isobutylmagnesium bromide. Per cent yields of both aldehyde and ketone increased in the order: ethylMgBr < n-proplylMgBr < n-butylMgCl < n-butylMgBr < isobutylMgBr. The results of the reactions of formic acetic anhydride, like those of the reactions of higher mixed acetic anhydrides, have been interpreted, principally, in terms of steric factors.

INTRODUCTION

Mixed carboxylic anhydrides have been investigated extensively in their reactions with alcohols and amines. These reactions are of interest because they show competition between the two halves of each mixed anhydride. For example, when an anhydride, $R'-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R$, is treated with an alcohol, R"OH, in an esterification reaction, either $R'-\overset{O}{\overset{\|}{C}}-O-R''$ or $R-\overset{O}{\overset{\|}{C}}-O-R''$ is formed preferentially.

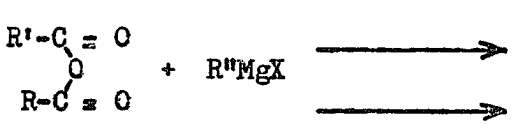
Studies of mixed anhydrides in the Friedel-Crafts reaction have been carried out recently in this laboratory (15, 27, 44). The mixed anhydrides were allowed to participate in a Friedel-Crafts acylation of benzene, in the presence of aluminum chloride catalyst. Reactions of mixed aliphatic anhydrides were carried out with anhydride, benzene, and catalyst in a 1:1:3 ratio. However, when either one or both of the radicals of the mixed anhydride was aromatic, it was necessary to use excess benzene, as solvent and reactant. The use of three parts of catalyst for each part of anhydride was practiced consistently.

Upon reaction of the mixed anhydride with benzene, a mixture of the two possible ketone products was usually formed, as follows:

$$\begin{matrix} R'-C(=O)-O-C(=O)-R \\ R-C(=O)-O-C(=O)-R' \end{matrix} + C_6H_6 \longrightarrow \begin{matrix} C_6H_5-\overset{O}{\overset{\|}{C}}-R' + RCOOH \\ C_6H_5-\overset{O}{\overset{\|}{C}}-R + R'COOH \end{matrix}$$

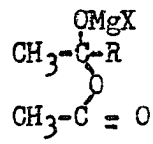
One of the two possible ketones was nearly always formed in predominance over the other; the molar ratios of the two ketones were determined by analysis of the reaction products. From the molar ratios of the two ketones, information concerning the influence of the two acyl groups of the mixed anhydride was obtained, that is, why certain anhydrides reacted in a given manner. The relative proportions of the ketones could usually be explained on the basis of a combination of steric and electronic factors; the results of the reactions of mixed aromatic anhydrides, carried out by the present author, in particular, could be explained in this manner (27). Friedel-Crafts reactions of mixed anhydrides are discussed in more detail on pages 11-14.

There has been no similar study of the behaviors of mixed anhydrides in the Grignard reaction. The closest approach to it has been some work with unsymmetrically substituted cyclic anhydrides, as described on pages 16-17 and pages 65-66. A mixed anhydride could react with a Grignard reagent in the two following manners:



Here, as in the Friedel-Crafts reaction, there could be produced either one of the two possible ketones, or a mixture of the two. However, in the Grignard reaction it is possible for the reaction to continue to give tertiary alcohols, with the Grignard reagent reacting further at the expense of the ketone products. Therefore, yields of ketones produced by the reaction of Grignard reagents with simple anhydrides were low, prior to the work of Newman and Booth in 1944 (31).

Newman and Booth added Grignard reagents to ether solutions of acetic anhydride at about -70° C., using a ratio of one mole of Grignard reagent to two moles of anhydride. Primary, secondary, and tertiary aliphatic and aromatic Grignard reagents gave 70-79 per cent yields of the corresponding methyl ketones, while allyl and benzyl reagents gave 42 and 52 per cent, respectively. With phenylmagnesium bromide and propionic anhydride a 59 per cent yield of propiophenone was obtained. Newman and Booth attributed the improved yields of methyl ketones to the stability at low temperatures of the complex



formed by the addition of one molecule of Grignard reagent to one of the carbonyl groups of acetic anhydride, and also to the decreased solubility of the complex at such temperatures. These eliminated, or greatly reduced, the opportunities for further reaction of the complexes with additional Grignard reagent, to form tertiary alcohols. At the low temperature involved there was probably no cleavage of the complex to form a ketone, which might react further.

The study of reactions of Grignard reagents with anhydrides at low temperatures was carried further by Newman and Smith (37). A solution of butylmagnesium[a] bromide was added to a solution of acetic anhydride in ether, at different temperatures. From the reflux temperature of ether to about -40° C. the yield of ketone

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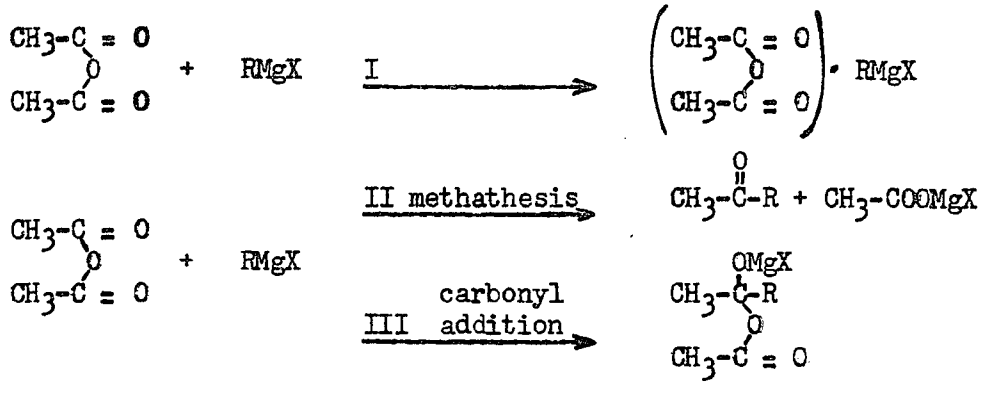
[a] Throughout this thesis, the terms butyl and propyl have been used to denote n-butyl and n-propyl, respectively.

remained almost constant at 50 per cent; but it increased upon further cooling, and reached 70 per cent in the vicinity of -70° C. Reactions at still lower temperature were not explored, because of the inconvenience involved. The temperature effect was about the same in the reaction of phenylmagnesium bromide with benzoic anhydride, and in the reaction of t-butylmagnesium chloride with acetic anhydride. Newman and Smith also studied the effects of variations from their standard technique, and the effects of further variation in the identities of the Grignard reagent and the anhydride. Primary, secondary, tertiary, and aromatic Grignard reagents gave high yields when they reacted with acetic, propionic, and butyric anhydrides at -70° C. With chloroacetic anhydride the yield fell to 35-50 per cent. Good yields of keto acids were obtained, using succinic anhydride.

It was pointed out by Newman and Smith that the mechanism of the reaction of Grignard reagents with acid anhydrides had not received much attention. As a Grignard reagent was added to an anhydride, a white precipitate formed. They suggested that this solid could be formed in any of three ways.



Summarized, their theory was as follows: The first step of the

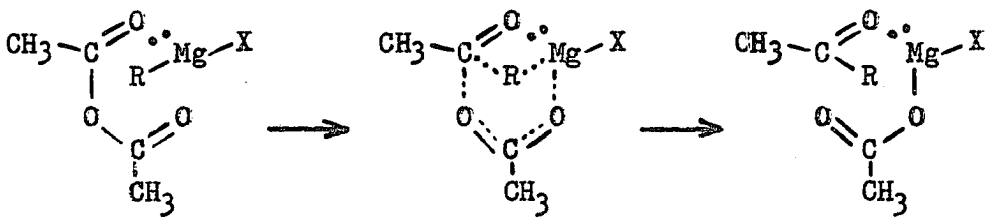
reaction was probably, in any case, represented by equation I, which represents a preliminary coordination of the Grignard reagent with the anhydride, the magnesium atom forming an oxonium-type complex with one of the oxygens of the anhydride. But treatment of the precipitate with ethyl alcohol did not lower the yield of ketone; therefore the reaction must have proceeded beyond the complex of equation I before the precipitate was formed.

If the reaction had proceeded by direct metathesis as in equation II, the precipitate would have been the bromomagnesium salt of the acid, and the free ketone would have been in the ether layer. Analysis of the clear supernatant ether solution showed only a trace of ketone. Therefore, mechanism II was incorrect.

The ketone was found to be held in the insoluble complex; therefore mechanism III, involving direct addition of the Grignard reagent to one of the carbonyl groups, fitted the experimental facts. The effect of the low temperature was apparently to stabilize the complex and prevent the formation of free ketone. This was shown by allowing the reaction mixture to warm to room temperature. The entire amount of ketone was then found to be in the ether solution. If the solution was cooled back to -70°, the ketone remained in the ether layer.

Kharasch and Reinmuth (24) agreed that the first step of the reaction was probably the formation of a complex as in equation I, and that the step was extremely rapid, and not rate-determining. It seemed likely to them that the complex formation took place at one of the carbonyl oxygen atoms. The conditions of the reaction

(slow addition of Grignard reagent solution to an excess of anhydride solution) appeared to argue against the probability of a trimolecular reaction mechanism. Kharasch and Reinmuth postulated that rearrangement of the original complex formed in equation I might lead to the formation of a relatively unstable intermediate compound by means of carbonyl addition. Thus the intermediate would take the form of a new complex involving a molecule of ketone and a molecule of magnesium salt.



The results of the work of Newman and Smith were consistent with the concept of Kharasch and Reinmuth.

It appeared to be of interest to prepare some mixed anhydrides and to allow them to react with Grignard reagents, following a procedure similar in most respects to that of Newman and Booth. It seemed probable that, at -70° C., a complex similar to that of simple anhydrides would be formed in the case of mixed anhydrides. Thus, the secondary reaction to give tertiary alcohols would be inhibited. The ketone yield would be increased to the point where a measurement of the relative proportions of the two possible ketones might lead to a correlation between the structures and the reactivities of the acyl radicals of the anhydrides.

Newman and co-workers added Grignard reagents to simple anhydrides in the ratio of 1 to 2, in order to decrease the possibility

of tertiary alcohol formation. The present author carried out some reactions using this 1:2 ratio, but results showed little or no difference from results of similar runs using equimolar quantities. Since the mixed anhydride was not easily attainable in large quantities, it would have been undesirable to waste half a mole of anhydride for each mole of the readily available Grignard reagent. Therefore, considering these factors, most of the present work was done using equimolar quantities of anhydride and Grignard reagent.

Anhydrides first chosen were acetic butyric, acetic valeric, acetic caproic, acetic isobutyric, acetic ∝-methylbutyric, and acetic isovaleric. The first three were selected to determine the effect of chain length, and the latter three provided branching on the alpha carbon and beta carbon. Phenylmagnesium bromide was the Grignard reagent chosen to react with these anhydrides, in ether solvent. In addition, acetic butyric anhydride was permitted to react with phenylmagnesium bromide in tetrahydrofuran solution, in order to show the effect of change of solvent. It would be expected that by taking place in tetrahydrofuran solution, the reaction would be less affected by steric hindrance. The effect of the solvent is discussed on page 57. Acetic butyric anhydride was also allowed to react with n-propylmagnesium bromide, in ether solution.

In view of the work done by Sibille on the Friedel-Crafts reaction with mixtures of simple anhydrides (described on page 13), it seemed desirable to make a study of the behavior of equimolar mixtures of two simple anhydrides in the Grignard reaction, using

ratios of 1 mole:1 mole:2 moles Grignard reagent. Anhydrides chosen for this purpose were acetic and butyric anhydrides, and acetic and valeric anhydrides--the same as those used by Sibille.

The reaction of formic acetic anhydride with Grignard reagents appeared to be of interest. The theoretical reaction product from the formic part of the anhydride would be an aldehyde, while the acetic part would produce a ketone. No evidence could be found in the literature of aldehydes having been prepared in this manner, although there are various other methods, discussed on pages 17-19, by which an aldehyde may be prepared from the corresponding Grignard reagent. Farrugia (15) and Sibille (44) attempted to obtain benzaldehyde from the reaction of formic acetic anhydride with benzene in the Friedel-Crafts reaction. A wide variety of reagents and conditions was used but no aldehyde was found in any of the products of reaction. It was decided to allow formic acetic anhydride to react with several Grignard reagents, both aromatic and aliphatic. Attempts at interpretation of results were carried out in a manner similar to that for the acetic higher-carboxylic acid anhydrides discussed above. The reaction of formic acetic anhydride with phenylmagnesium bromide was carried out in both ether and tetrahydrofuran solvent. Other aromatic Grignard reagents used, all in ether solvent, were o-, m-, and p-tolylmagnesium bromides, and m-chlorophenylmagnesium bromide. Aliphatic Grignard reagents used were ethyl-, propyl-, butyl-, and isobutylmagnesium bromides. Any alcohols formed from further reaction of these Grignard reagents with the carbonyl products could also be determined analytically,

and considered along with the carbonyl products of reaction. Thus the total of the products from the formic part of the anhydride might be compared with the total from the acetic part.

It also appeared to be of interest to carry out the Grignard reactions of acetic butyric and formic acetic anhydrides with phenylmagnesium bromide at 0° C., in order to compare the results at that temperature with results at the very low temperature.

REVIEW OF THE LITERATURE

The first mixed carboxylic acid anhydride reported was acetic benzoic anhydride. This was prepared in 1852 by Gerhardt (20, 21), by the reaction of acetyl chloride with sodium benzoate. He prepared five other mixed anhydrides in the same manner. Upon heating, they disproportionated into a mixture of the two simple anhydrides.

Autenrieth in 1887 (1) discovered that mixed anhydrides could be produced by refluxing a mixture of an organic acid with acetic anhydride. He prepared acetic benzoic anhydride in this manner, along with several others. These anhydrides distilled over ranges of more than 10 degrees. Behal (4, 5) prepared formic acetic anhydride by a similar method, heating a mixture of 3 moles of formic acid and 4 moles of acetic anhydride at 50° C. for one hour, then collecting the anhydride distilling at 29° C. at 17 mm. pressure. Different methods of preparation of mixed anhydrides were reported by Bougault (9), and by a British patent issued in 1913 (51). In 1952, Hurd and Dull (25) prepared mixed acetic anhydrides by the interaction of ketene and acids. This method is commonly used today.

Many investigators studied the reaction products formed when mixed anhydrides were permitted to react with amines, alcohols, and phenols. Behal allowed formic acetic anhydride to react with both amines and alcohols, and obtained only the formic derivatives. On

warming with phenols, acetates, and not formates, were obtained (6, 7). In 1942, Edwards and Reeves (13) carried out the reaction of formic acetic anhydride and furfuryl alcohol. Furfuryl formate, which could not be prepared by more common methods, was obtained; but no furfuryl acetate was observed in the reaction products. Also, Hurd and co-workers (24, 26) obtained formyl derivatives exclusively upon the reactions of formic acetic anhydride with aniline, and with nitro alcohols. On the other hand, acetic esters were produced exclusively if sulfuric acid was present as a catalyst or if the reaction mixture was heated.

The reaction of an amine with an acid anhydride or acid chloride was shown by Williams and Hinshelwood (88) to be a heterolytic reaction in which the amine acted as a nucleophilic reagent and the anhydride or acid chloride as an electrophilic reagent. Emery and Gold (14) discussed the reaction products of an amine with a mixed anhydride, considering both electronic and steric factors.

The first time that mixed anhydrides were studied in the Friedel-Crafts reaction was in 1932, when Zeavin and Fisher (54) carried out the reaction of benzene with a series of mixed all-aromatic anhydrides, prepared by the reaction between one acid and the acyl chloride of the other, in the presence of pyridine. When benzoic mono-m- nitrobenzoic anhydride was used, the formation of a trace of mono-m-nitrobenzophenone was observed, but in all other cases, only benzophenone was reported; yields ranged from 60 to 88 per cent with the various anhydrides. The reactions took

place at steam bath temperature, in benzene solution, with a ratio of 2 moles of aluminum chloride per mole of anhydride. Zeavin and Fisher appear to have devoted nearly all of their interest and efforts to the identification and separation of the one major ketonic product, in each of their experiments. Their failure to obtain any of the other possible ketones, in every instance except one, did not necessarily mean that such compounds were not formed in minor quantities.

Williams, Dickert, and Krynitsky (53) used ketene to prepare a series of nine mixed acetic anhydrides, all aliphatic except one: propionic, butyric, isobutyric, valeric, isovaleric, trimethylacetic, caproic, stearic, and benzoic. Friedel-Crafts reaction of these took place in excess benzene, as reactant and solvent, with a 3:1 ratio of $AlCl_3$ to anhydride, and at steam bath temperature. The lower molecular weight ketone was the favored product in the cases of propionic, trimethylacetic, stearic, and benzoic anhydrides. Farrugia (15) also studied a series of mixed anhydrides in the Friedel-Crafts reaction. Using carbon disulfide as solvent, operating at 0-5° for three hours, and with the anhydride, benzene, and catalyst in a 1:1:3 ratio, he found that the higher molecular weight ketone was usually formed in greater quantity than the lower. His results showed that the predominance of higher molecular weight ketones over lower molecular weight ketones varied from strong to slight, depending largely, in his opinion, upon the relative acid strengths and steric hindrances. In the case of formic acetic anhydride, which he used under a wide variety of conditions, only the acetyl derivative was found, with no aldehyde formation observed.

Sibille (44) followed up Farrugia's work by studying the reactions of a series of five mixed acetic anhydrides. He, like Farrugia, attempted to correlate the results with the structural characteristics of the acyl radicals involved. Sibille's work also included a comparison of the reactions of equimolar mixtures of acetic anhydride and valeric anhydride with the reaction of the acetic valeric anhydride, and a similar comparison involving acetic and butyric anhydrides and acetic butyric anhydride. Reactions were carried out at 0° C., by the addition of one part benzene to either one part of the mixed anhydride, or one-half parts of each of the simple anhydrides, in carbon disulfide solvent. Slightly more than three parts aluminum chloride catalyst were used. Relative proportions of the products differed significantly; this appeared to prove, among other things, that reaction of the mixed anhydride did not take place by means of disproportionation into a mixture of the two simple anhydrides, or into two aluminum chloride complexes. Sibille was the first of the workers mentioned here to use gas chromatography to estimate relative yields of the two ketones, with consequently more reliable results than earlier workers could obtain, in most cases, by separating their reaction products by distillation or recrystallization.

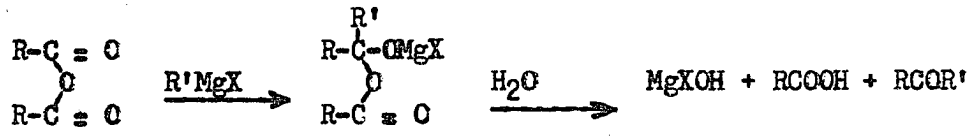
In view of the fact that the work of Zeavin and Fisher was inconclusive with respect to the relative amounts of the two possible ketonic products, the higher molecular weight ketone having been identified by them in only one case, the present author (27), in a problem preceding the present one, carried out a further study

of mixed aromatic anhydrides in the Friedel-Crafts reaction. Excess benzene was used as solvent and reactant, and slightly over three parts of $AlCl_3$ was used per mole of anhydride. In addition to the reactions of four mixed all-aromatic anhydrides, the reactions of three acetic aromatic anhydrides were studied. The relative proportions of the ketones obtained were explained on the basis of a combination of steric and electronic factors. In addition, parallelling Sibille's work with mixtures of simple anhydrides, a comparison was made of the reaction of benzene with a mixture of benzoic and p-nitrobenzoic anhydrides with the reaction of benzene with benzoic mono-p-nitrobenzoic anhydride. The results were similar in principle to the results of Sibille.

The first use of carboxylic acid anhydrides in the Grignard reaction was reported by Tissier and Grignard in 1901 (49). They added ether solutions of acetic and benzoic anhydrides to ethereal methylmagnesium iodide cooled in ice, and obtained tertiary alcohols. Reactions of phthalic anhydride and Grignard reagents were studied in 1904 by Pickles and Weizmann (39) and by Bauer (2). Pickles and Weizmann obtained the keto acids, among various products, and Bauer identified diketones. There are several other possible products of reaction of cyclic anhydrides, including phthalic, with Grignard reagents. These reactions have been outlined by Kharasch and Reinmuth in their book, "Grignard Reactions of Nonmetallic Substances."

Fournier in 1904 (18) carried out a study of the reactions of anhydrides with Grignard reagents at a low temperature (about -20°), using high dilution and reverse addition (addition of Grignard

reagent to the anhydride solution). He reported that the reaction products from the reaction of $(RCO)_2O$ and R'MgX contained the acid RCOOH, the ketone RCOR', and small amounts of tertiary alcohol, $RC(OH)R'_2$. Fournier formulated the reaction as:



Anhydrides used were acetic, propionic, butyric, isobutyric, isovaleric, and heptanoic. A variety of aliphatic Grignard reagents were used, including both bromides and chlorides.

The reactions of many other symmetrical anhydrides with Grignard reagents have been investigated under various conditions, by many workers, and have been listed by Kharasch and Reinmuth (28). Ketone yields obtained by workers using non-cyclic anhydrides, such as acetic anhydride, did not exceed 56 per cent, and were generally not more than 45 per cent. No significant improvement in the yields of ketones was made until the work of Newman and Booth in 1944 (31). They carried out the reactions of Grignard reagents with anhydrides, mainly acetic anhydride, at about -70° C., as was previously described on pages 2-3. Using acetic anhydride and a variety of Grignard reagents, 70 to 79 per cent yields of the ketones were obtained. This method of ketone preparation was also used successfully by other workers at Ohio State University (11, 34) and by Champaigne and Reid (12). The study of reactions of Grignard reagents with anhydrides at low temperatures was carried further by Newman and Smith, as discussed on pages 3-5 (37). They studied

the effect of variation in the temperature of reaction, the effect of variation from the standard technique, and the mechanism of the reaction.

There has been considerable work done with the Grignard reactions of unsymmetrical cyclic anhydrides, starting with that of Bauer in 1911 (3), but as Scheurer (43) pointed out, very little careful quantitative work has been done. In most cases the product, theoretically consisting of a mixture of two keto acid isomers, was not separated into its components because of experimental difficulties. Some of the more valid examples of this type of work were the reactions of Grignard reagents with 1,2-naphthalic anhydride (17, 35). Upon the reaction of this anhydride with either phenylmagnesium bromide or p-chlorophenylmagnesium bromide, 41 per cent yield of a crude mixture of keto acids was obtained; 24 per cent of this was formed by reaction at the 1-carbonyl carbon and 76 per cent from reaction at the 2-carbonyl carbon. The reaction at the carbonyl carbon adjacent to the substituent appeared to be inhibited. The reaction of o-tolylmagnesium bromide at the 1-carbonyl was even more greatly inhibited, giving only 7 per cent reaction at the 1-carbonyl carbon and 93 per cent at the 2-carbonyl carbon, with a total keto acid yield of 46 per cent. Thiophene-magnesium iodide (41) also reacted predominantly at the 2-carbonyl carbon. 3,4-Dimethylphthalic anhydride, upon reacting with the Grignard reagent from 3-bromo-o-xylene (38), gave 79 per cent reaction at the 1-carbonyl carbon and 21 per cent at the 2-carbonyl carbon.

In 1937, Newman (30) carried out the reaction of 3-methylphthalic anhydride with 1-naphthylmagnesium bromide. Total yield of keto acid was 53 per cent, with 96 per cent of this formed by reaction at the 1-carbonyl carbon and only 4 per cent at the 2-carbonyl carbon. 3-Methylphthalic anhydride was allowed to react with phenylmagnesium bromide (32), and with m-xylylmagnesium bromide and mesitylmagnesium bromide (33). Newman and Scheurer (36) then decided to see what effect the substitution of a chlorine atom for a methyl group in the anhydride might have. Results of their reactions of 3-chlorophthalic anhydride with phenyl-, m-xylyl-, and mesitylmagnesium bromides, along with the results of the previous work with 3-methylphthalic anhydride, have been listed and discussed on pages 65-66.

Several methods have been recorded for accomplishing the conversion of a Grignard reagent, RMgX, to the corresponding aldehyde, RCHO. The problem was pursued largely in the first decade of this century. In 1903, Gattermann and Maffezzoli (19) found that at -50° C. an excess of ethyl formate reacted with Grignard reagents to give products consisting largely of aldehydes, rather than the secondary alcohols formed by further reaction. Bouveault (10) used disubstituted formamides as a means of converting Grignard reagents into aldehydes. This reaction, however, in many cases produced tertiary amines as the main product, and Bouveault did not give exact yields of his aldehyde products. An aldehyde synthesis was reported involving addition of a Grignard reagent to an isocyanide (40), but was successful only in the case of phenylmagnesium bromide and methyl

isocyanide. In 1904, a means of synthesizing aldehydes from ethyl orthoformate and the Grignard reagent was discovered independently by Bodroux (8) and Tschitschibabin (50). The reaction was greatly affected by slight differences in procedure, and yields of aldehydes prepared by this method have varied widely (46). Aldehydes have been prepared in small yields from formic acid and Grignard reagents (55, 23). The salts of formic acid were tried, but the yields were very poor.

A good method of synthesis was discovered by Monier-Williams in 1906 (29), in which the Grignard reagent was allowed to react with ethoxymethyleneaniline. Yields ranged from 30 to 60 per cent. In another method, aromatic aldehydes were prepared by means of the reaction of Grignard reagents with chloral (42). Secondary trichloroalcohols were formed, transformed into hydroxy acids by action of alkali, and converted to aldehydes by heating with aqueous potassium carbonate.

Wuyts and co-workers developed a synthesis in which a Grignard reagent reacted with carbon disulfide to produce a dithio acid. The dithio acid was converted into an aldehyde derivative by the action of semicarbazide, phenylhydrazine, or hydroxylamine, and the aldehyde derivative hydrolyzed to the aldehyde. This synthesis, along with other aldehyde syntheses, has been discussed by Smith and Nichols (47). By a consideration of the results in the literature they concluded that the most promising methods, as far as yields and general applicability were concerned, were the syntheses from ethyl orthoformate, from ethoxymethyleneaniline, and from the dithio acid.

Smith and Nichols prepared a series of eight methylated aromatic aldehydes by each of these three methods, and compared the yields of aldehydes, and the difficulties involved in each method. The ethoxymethyleneaniline synthesis gave yields ranging from 60 to 82 per cent, 4 to 17 per cent higher than those obtained by the orthoformate method. The dithio acid synthesis was distinctly inferior to both of the other methods.

Another method for the preparation of aldehydes from the corresponding Grignard reagent has been described recently by Stiles and Sisti (45, 48). They allowed the Grignard reagent to react with p-dimethylaminobenzaldehyde to form a secondary alcohol. The alcohol was subsequently cleaved by an electrophilic reagent, such as diazotized sulfanilic acid, to give the aldehyde. Yields ranged from 50 to 82 per cent. The reaction was relatively insensitive to steric and electronic effects in the aldehyde, and worked almost equally well for aliphatic and aromatic aldehydes.

EXPERIMENTAL PART

APPARATUS

Pyrolysis of Acetone

Ketene was generated in apparatus similar to that described by Fieser and Fieser (16). A gas washing type absorption vessel was used, allowing the gas to bubble through a high level of liquid before escaping. The heating coil was made of chromel "A" wire. The rate of production of the ketene was determined by allowing the ketene to react with a known excess of sodium hydroxide, and titrating with standard acid using phenolphthalein as indicator.

Grignard Reagent Preparations

A 500 ml. round-bottom flask was equipped with a mechanical stirrer, reflux condenser, and a dropping funnel. The dropping funnel and condenser were protected by calcium chloride tubes. The reaction flask was sometimes heated in a water bath or cooled in an ice-water mixture.

Grignard Reactions

A 500 ml. round-bottom flask, equipped with a mechanical stirrer, calcium chloride drying tube, and a dropping funnel, was used. The dropping funnel was protected by a calcium chloride tube. The flask was immersed in a mixture of Dry Ice and acetone

in a Dewar flask; or, when reactions were carried out at 0° C., in an ice-water mixture.

Chromatographs

Analyses of most samples were carried out by means of a Beckman GC-2 gas chromatograph with a 6 ft. 20 per cent Silicon SF 96 on 30/60 Silocel column, after calibration using a standard mixture of the reaction products expected to be present. The standards were in most cases analyzed with an error of not more than one per cent.

Analysis of the products of reaction of formic acetic anhydride with m-chlorophenylmagnesium bromide was carried out by means of a Barber Colman IDS Chromatograph Model 20 with a 200 ft. Apiezon L capillary column.

Fractionating Columns

Two vacuum-jacketed Vigreux-type columns of different sizes were employed. The one most often used was 9 cm. high, and 11 mm. in diameter, and the other, used for very small quantities but not as efficient in separation, was 5 cm. high and 7 mm. in diameter.

SOURCES AND PURIFICATION OF STARTING MATERIALS

Before use in preparation of Grignard reagents and in Grignard reactions, Mallinckrodt anhydrous ether was dried and stored over sodium. Untreated ether was used in extractions of the aqueous layers.

Matheson, Coleman, and Bell tetrahydrofuran was distilled and the fraction boiling at 65-66° was used.

Mallinckrodt analytical reagent grade acetone was used in the preparation of ketene. Mallinckrodt anhydrous sodium sulfate and calcium chloride and other inorganic reagents were used for drying and various other purposes.

Matheson, Coleman, and Bell reagent grade organic acids were used without further purification.

Eastman, Matheson, Coleman, and Bell, and J. T. Baker aromatic and aliphatic halides were dried with anhydrous sodium sulfate, before use in preparation of Grignard reagents.

Fisher magnesium metal turnings were washed with ether and dried at 100-120°, before use in Grignard reagent preparation.

Mallinckrodt acetic anhydride was distilled at 44 mm. pressure and the fraction boiling at 60.5-62° was collected for use in Grignard reactions.

Eastman butyric anhydride was distilled at 10 mm. pressure and the fraction boiling at 60-61° was collected for use in Grignard reactions.

Valeric anhydride was prepared by a method similar to that outlined on page 374 in Vogel (52). Valeric acid was first acetylated with ketene. Using an oil bath, the reaction mixture was heated to 220° over a period of one hour and maintained at 220° for 3 hours while acetone, ketene, and acetic acid were removed. The mixture was then distilled at 15 mm. pressure. The fraction distilling at 110-114° was redistilled and the fraction from the second distillation boiling at 110-112° was used in the Grignard reaction.

Matheson, Coleman, and Bell, J. T. Baker, and Fisher ketones and aldehydes were distilled for use as chromatographic standards. Fisher secondary alcohols were distilled for use as chromatographic standards.

Fisher ketones were used for preparation of tertiary alcohols used for chromatographic standards. The tertiary alcohols were prepared by the reaction of a Grignard reagent with the appropriate ketone, and were purified by distillation.

METHODS OF PREPARATION

Mixed Acetic Anhydrides (Other Than Formic)

All mixed anhydrides, except formic acetic anhydride, were prepared by acetylation of the appropriate carboxylic acids with ketene (25). All of the acids used were liquids, and slightly more than the theoretical amount of ketene was passed directly into them. The absorption vessel was immersed in an ice-water bath throughout the passage of ketene, because the reactions of the acids with ketene were exothermic, and because mixed anhydrides had a tendency to disproportionate at high temperatures.

When acetylation was complete, the anhydride was poured into a flask, and the flask, while cooled in ice, was evacuated to about 45 mm. pressure by means of a water aspirator. This reduced pressure was maintained for about ten minutes, in order to remove excess ketene and any other volatile impurities. The anhydride was then washed in a separatory funnel with cold (0-5°) 10 per cent sodium carbonate solution until no further evolution of gas could be detected. Three washings with approximately 100 ml. portions of carbonate solution

were usually sufficient. The anhydride was separated from the aqueous layer, and dried with anhydrous calcium chloride. Samples were taken for titration to determine neutralization constants, and for refractive index measurements. The anhydride was not distilled, but was used immediately in the Grignard reaction.

Formic Acetic Anhydride

Formic acetic anhydride was prepared in two ways. In the first method, first used by Behal (4, 5) and modified somewhat by Edwards and Reeves (13), a mixture of acetic anhydride and formic acid in a 4:3 molar ratio was heated under reflux for one hour at 50°. The mixture was then distilled at 45 mm. pressure and a fraction collected at 43-47°. This fraction was washed with petroleum ether to remove impurities, and distilled again at 45 mm. The fraction collected at 44-46° was used in the Grignard reaction, after samples were taken for titration, and for refractive index measurement.

The formic acetic anhydride used in the majority of runs was prepared by acetylation of formic acid with ketene. Slightly more than the theoretical amount of ketene was passed into the formic acid, in an absorption vessel immersed in an ice-water bath, as for the other anhydrides. As before, the anhydride was poured into a flask and the flask evacuated for about ten minutes. However, instead of washing, which caused disproportionation, the anhydride was distilled at 45 mm. pressure, and the distillate collected at 44.5-46.5° used in the Grignard reaction.

Samples of anhydride from each run were sealed and stored in glass tubes. A sample prepared about four months earlier by the ketene method was sent for carbon and hydrogen analysis. The analyst commented in his reply that they were unable to run an analysis on the sample, because the sample exploded as the technician opened the tube. He commented that possibly peroxide formation had taken place. A recently prepared sample was sent for analysis; the same difficulty was found, therefore no analyses were obtained.

Preparation of Grignard Reagents

Grignard reagents were prepared by methods similar to those outlined in Vogel (52), pages 257 and 756. The procedures for preparation of aliphatic and aromatic Grignard reagents were slightly different. For both types, magnesium and a small crystal of iodine were placed in the reaction flask. In the preparation of aromatic Grignard reagents, about 15 ml. of the aromatic halide and 20 ml. of ether were also placed in the flask, and the reaction was started by refluxing on a water bath. After the reaction began, the remainder of the halide, in about 125 ml. of ether, was added gradually to the reaction vessel. In the preparation of aliphatic Grignard reagents, about 150 ml. of ether was present in the reaction flask at the start, and the reaction was started by running about 15 ml. of an ether solution of the halide into the reaction flask; this was followed by gradual addition of the remainder of the halide solution, with cooling in an ice-water mixture. Heating was not necessary for starting the reaction, except in the preparation of butylmagnesium chloride.

In the preparation of aromatic Grignard reagents, after addition was complete, the reaction mixture was refluxed on a water bath for 30 minutes. In the preparation of aliphatic reagents, stirring was continued for 15 minutes after addition, without heating.

The strengths of the Grignard reagents were determined by the acid titration method (22). A 5 ml. portion of the Grignard reagent was added to water, liberating base. An excess of standard acid was added to react with the liberated base, followed by back titration of the excess acid with a standard base solution. The Grignard reagent was stored in a desiccator for the short time (usually 1-2 hours) during which preparation of the mixed anhydride was being completed.

GRIGNARD REACTIONS (GENERAL PROCEDURE)

The Grignard reagent was added dropwise over a period of one hour (about 0.2 moles/hour) to a solution of the anhydride in about 120 ml. of ether (or in tetrahydrofuran, in Runs 22-24 and 59-61), cooled to -78° C. The reaction was allowed to proceed for two hours after addition was complete; stirring was continued throughout. The reaction mixture was then allowed to warm to about -10° C.; it was hydrolyzed with saturated aqueous ammonium chloride solution, and the two-phase system transferred to a separatory funnel. The aqueous layer was removed, and the ether solution was washed twice with five per cent sodium hydroxide solution and once with saturated sodium chloride solution. The washings were extracted with ether, the extracts added to the original ether solution, and the resulting total ether solution dried with anhydrous sodium sulfate. In most

cases, after filtration, ether was distilled off until the solution reached a volume of 75-100 ml., from which two samples of about 0.02 ml. each were analyzed by means of the gas chromatograph. In some cases, where chromatographic examination of one or more runs dried with anhydrous sodium sulfate (or not dried at all) showed that no alcohols were present in appreciable quantity, calcium chloride was used as a drying agent in some of the checking runs made from the same materials.

The relative proportions of the two main reaction products (two ketones, or ketone and aldehyde), determined from chromatographic data, were reasonably accurate. Standard ether (or tetrahydrofuran) solutions containing compounds corresponding to products of each type of reaction were analyzed. These solutions contained known quantities of the two main carbonyl products, and appropriate amounts of any impurities, such as unreacted halides from preparation of the Grignard reagents, which were present in the corresponding experimental run. In all cases, the proportions of the carbonyl compounds in the standard solutions, calculated from chromatographic data, were within one per cent of the known values. Chromatographic determination of the relative proportions of four compounds, when two alcohols were present in the standard solution in addition to the two carbonyl compounds, was somewhat less accurate. However, accuracy in determination of the relative proportions of the two carbonyl compounds considered alone remained the same as when the alcohols were not present.

The determination of the absolute quantities of the reaction products was appreciably less accurate than was the determination

of the relative proportions. Since the present author was most interested in the relative proportions, these were determined in most cases before distillation of the products, avoiding any possible losses or errors caused by such distillation. The absolute quantities were then estimated by collecting and weighing the material distilling over the entire range of the boiling points of the main reaction products. The quantity of each product was calculated from the previously determined relative proportions. In several cases, material other than the main reaction products was also collected in the given range. Quantities of these compounds were therefore determined also. Examples may be found in the descriptions (pages 29-45) of the various types of reactions.

In the products of a few types of Grignard reactions there was no volatile fraction higher than the higher-boiling carbonyl compound, making complete recovery of this ketone by distillation unsatisfactory. The carbonyl titration method was therefore used in such situations. An excess of hydroxylamine hydrochloride solution was permitted to react with an aliquot solution of the reaction products, and the liberated hydrogen chloride was titrated with standard sodium hydroxide solution. From the total moles of carbonyl compounds calculated to be present, and from gas chromatograph data, the quantities of the two ketones were determined.

Attempts to determine the ketone ratios by quantitative fractional distillation of the products showed this method to be impractical, or at best less accurate than chromatographic estimation. It was necessary, however, to separate some of each product, in order

to identify it positively. Samples of the aldehydes and ketones were collected at their characteristic boiling points, and refractive index measurements were taken. Two derivatives of each were prepared, with the exception of the few cases where only one derivative was reported in the literature. In addition, elemental analyses of aldehydes were carried out. Alcohols were identified by means of their retention times on the gas chromatograph, and in some instances by their characteristic boiling points, and by melting points of derivatives.

Three or more checking runs were made for most reactions. Exceptions, in which just two runs were made, were: the reaction of formic acetic anhydride with phenylmagnesium bromide when large quantities of starting materials were used; the reaction of formic acetic anhydride with p-tolylmagnesium bromide, using a 2:1 molar ratio of anhydride to Grignard reagent; and the reaction of formic acetic anhydride with butylmagnesium chloride, the only one involving a chloride. In the following pages (29-45), a run illustrating each type of reaction has been described, with mention of any variations from the general procedure. All temperatures have been expressed in degrees centigrade.

GRIGNARD REACTIONS OF MIXED CARBOXYLIC ANHYDRIDES

Acetic Butyric Anhydride -- Phenylmagnesium Bromide: Runs 1-6

Run No. 2

Anhydride - 17.9 g. (0.138 moles). Grignard reagent - 0.138 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	6.11 g.	0.0509	36.8	65.1
butyrophenone	4.04 g.	0.0273	19.8	34.9

Distillation at 20 mm. pressure over the range 89-121° C. gave 10.15 g. of product. This was calculated from chromatographic data to contain 6.11 g. acetophenone and 4.04 g. butyrophenone. Upon further distillation, samples of acetophenone and butyrophenone were collected at 91-93° and 115-117°, respectively.

Acetic Valeric Anhydride - Phenylmagnesium Bromide: Runs 7-9

Run No. 7

Anhydride - 30.1 g. (0.209 moles). Grignard reagent - 0.209 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	9.73 g.	0.0810	38.6	64.4
valerophenone	7.37 g.	0.0454	21.7	35.6

Distillation at 20 mm. over the range 89°-132° C. gave 17.10 g. of product. Samples of acetophenone and valerophenone were collected at 91-93° and 127-129.5°, respectively.

Acetic Caproic Anhydride - Phenylmagnesium Bromide: Runs 10-12

Run No. 10

Anhydride - 31.75 g. (0.200 moles). Grignard reagent - 0.200 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	8.90 g.	0.0740	36.9	61.6
caprophenone	8.18 g.	0.0465	23.4	38.4

Distillation was carried out over the range 89-100° at 20 mm. The pressure was then reduced to 14 mm., and distillate collected up to 139° C. The total distillate collected was 18.41 g.; however, 1.33 g. of this was calculated by chromatographic data to be biphenyl,

a by-product of the preparation of the Grignard reagent. The biphenyl was collected between the boiling ranges of acetophenone and caprophenone. A sample of biphenyl was collected at 128-130° at 14 mm. pressure. It solidified in the receiving flask and was identified by its melting point (69-71°), mixed melting point, and comparison of chromatograph retention time with that of a known sample of biphenyl. Samples of acetophenone and caprophenone were collected at 91-93° at 20 mm., and 134-136° at 14 mm., respectively.

Acetic Isobutyric Anhydride - Phenylmagnesium Bromide: Runs 13-15

Run No. 13

Anhydride - 21.0 g. (0.162 moles). Grignard reagent - 0.162 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	6.66 g.	0.0555	34.3	69.9
isobutyrophenone	3.52 g.	0.0238	14.7	30.1

Distillation at 20 mm. over the range 89-113° gave 10.18 g. of product. Samples of acetophenone and isobutyrophenone were collected at 91-93° and 106-108°, respectively.

Acetic α-Methylbutyric Anhydride - Phenylmagnesium Bromide: Runs 16-18

Run No. 17

Anhydride - 17.0 g. (0.118 moles). Grignard reagent - 0.118 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	6.45 g.	0.0536	45.4	76.1
α-methylbutyrophenone	2.72 g.	0.0168	14.2	23.9

Distillation at 20 mm. over the range 89-122° C. gave 9.17 g. of product. Samples of acetophenone and α-methylbutyrophenone were collected at 91-93° and 116-118°, respectively.

Acetic Isovaleric Anhydride - Phenylmagnesium Bromide: Runs 19-21

Run No. 19

Anhydride - 14.4 g. (0.100 moles). Grignard reagent - 0.100 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	4.80 g.	0.0400	40.0	67.0
isovalerophenone	3.17 g.	0.0196	19.6	33.0

Distillation at 20 mm. over the range 89-125° gave 7.97 g. of product. Samples of acetophenone and isovalerophenone were collected at 91-93° and 119-121°, respectively.

Acetic Butyric Anhydride - Phenylmagnesium Bromide; Tetrahydrofuran Used as Solvent, in Place of Ether: Runs 22-24

Run No. 23

Anhydride - 17.5 g. (0.135 moles). Grignard reagent - 0.135 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	7.10 g.	0.0592	43.9	62.9
butyrophenone	5.19 g.	0.0350	25.9	37.1

As with previously-described runs (Nos. 1-6) involving these two products, distillation was carried out at 20 mm. pressure over a range of 89-121°. Samples of the products were obtained as before.

Acetic Butyric Anhydride - Propylmagnesium Bromide: Runs 25-27

Run No. 27

Anhydride - 15.3 g. (0.118 moles). Grignard reagent - 0.118 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
methyl propyl ketone	3.44 g.	0.0400	33.9	56.6
dipropyl ketone	3.50 g.	0.0307	26.1	43.4

Recovery of the total yield of ketones by distillation was unsatisfactory. A 10 ml. aliquot portion of the 52.5 ml. ether solution of reaction products was taken, and the carbonyl titration method was used, as described on page 28. From the total moles of carbonyl products shown to be present, and from gas chromatograph data, the quantities of the two ketones were determined. The 42.5 ml. of solution remaining (after titration of the 10 ml. aliquot) was distilled at atmospheric pressure. Samples of methyl propyl ketone and dipropyl ketone were collected at 101-103° and 143-144°, respectively.

Acetic and Butyric Anhydrides - Phenylmagnesium Bromide: Runs 28-30

Run No. 28

Acetic anhydride - 8.89 g. (0.0871 moles).

Butyric anhydride - 13.79 g. (0.0871 moles). Grignard reagent - 0.1742 moles

	Total Yield	Moles	Per cent Yield	Moles Per cent of Total Ketones
acetophenone	7.76 g.	0.0645	37.1	62.8
butyrophenone	5.57 g.	0.0378	21.5	37.2

A procedure similar to that employed for the reaction of acetic butyric anhydride with phenylmagnesium bromide (Runs 1-6) was followed in this run.

Acetic and Valeric Anhydrides - Phenylmagnesium Bromide: Runs 31-33

Run No. 31

Acetic anhydride - 7.15 g. (0.0698 moles).

Valeric anhydride - 13.0 g. (0.0698 moles). Grignard reagent - 0.1396 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	6.75 g.	0.0563	40.2	65.5
valerophenone	4.85 g.	0.0300	21.4	34.5

A procedure similar to that employed for the reaction of acetic valeric anhydride with phenylmagnesium bromide (Runs 7-9) was followed in this run.

Formic Acetic Anhydride - Phenylmagnesium Bromide: Runs 34-44

Run No. 37

Anhydride - 13.9 g. (0.158 moles). Grignard reagent - 0.158 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
benzaldehyde	6.00 g.	0.0564	35.8	82.7
acetophenone	1.42 g.	0.0118	7.4	17.3

Chromatographic analysis of the ether solution of reaction products gave the relative proportions of the products. Unreacted bromobenzene from the preparation of the Grignard reagent could not be separated cleanly from benzaldehyde except by fractional distillation. The products were therefore distilled at 20 mm., and

collected over the range 45°-105°. Chromatographic data showed the presence of 1.82 g. of bromobenzene, in addition to the above quantities of benzaldehyde and acetophenone. Upon further distillation, a sample of benzaldehyde was collected at 179-180° at atmospheric pressure, and a very small sample of acetophenone was collected at 91-92° at 20 mm. pressure.

Run No. 40

Anhydride - 72.7 g. (0.827 moles). Grignard reagent - 0.827 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
benzaldehyde	26.12 g.	0.2460	29.8	91.4
acetophenone	2.78 g.	0.0231	2.8	8.6

The quantities of the starting materials were about five times as great as those used in the other runs. The reaction was carried out in the same general manner as for previous runs, with minor exceptions. A one liter reaction flask was used instead of the 500 ml. flask; the Grignard reagent was added during a period of 2-1/2 hours, and the reaction allowed to continue for 2 hours after addition was complete. The above figures were obtained in the same manner as for Run 37; chromatographic data were applied to the distillate collected over the range 46-107° at 20 mm. (39.2 g.). 10.3 g. of bromobenzene was shown to be present.

An attempt was made to recover the benzaldehyde by distillation. The following fractions were taken throughout the distillation, as the temperature rose from 46° to 105°.

A: 46-50° - 2.7 g.

B: 50-67° - 11.0 g.

C: 67-75° - 22.5 g.

D: 75-105° - 3.0 g.

Fraction B was redistilled; its higher boiling part (67-70°) weighed 2.05 g. and was combined with fraction C of the first distillation, giving a total of 24.55 g. of crude benzaldehyde. This was redistilled, giving 20.5 g. of product collected from 69° to 72° (reported value at 20 mm. is 70-71°). This benzaldehyde was found to have a refractive index of 1.5469 at 20° (reported value is 1.5453). On further redistillation, at atmospheric pressure, 14.2 g. was collected over the range 179-180°. The refractive index at 20° of this sample was 1.5456.

Formic Acetic Anhydride - o-Tolylmagnesium Bromide: Runs 45-47

Run No. 45

Anhydride - 10.55 g. (0.121 moles). Grignard reagent - 0.121 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
o-methylbenzaldehyde	3.70 g.	0.0308	25.4	97.0
o-methylacetophenone	0.13 g.	0.0010	0.8	3.0

Chromatographic analysis gave the relative proportions of the reaction products. Unreacted o-bromotoluene from the preparation of the Grignard reagent interfered with the separation of the aldehyde by distillation; therefore, material distilling over the range 55-100° at 10 mm. pressure was collected, and absolute quantities determined from chromatographic data. The above figures for the aldehyde and ketone were obtained in this way; in addition,

1.9 g. of o-bromotoluene was shown to be present. A sample of the aldehyde was collected at 92-94° at 10 mm. The ketone was present in too small a quantity to be separated.

Formic Acetic Anhydride - m-Tolylmagnesium Bromide: Runs 48-50

Run No. 50

Anhydride - 10.6 g. (0.121 moles). Grignard reagent - 0.121 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
m-methylbenzaldehyde	4.93 g.	0.0410	33.9	97.4
m-methylacetophenone	0.15 g.	0.0011	0.9	2.6

Material distilling over the range 60-105° at 12 mm. pressure, including unreacted m-bromotoluene from Grignard reagent preparation, was collected, and chromatographic techniques applied. In addition to the above quantities, 1.6 g. of m-bromotoluene was shown to be present. A sample of the aldehyde was collected at 93-94° at 17 mm. Not enough ketone was present to permit separation.

Formic Acetic Anhydride - p-Tolylmagnesium Bromide: Runs 51-55

Run No. 51

Anhydride - 10.6 g. (0.121 moles). Grignard reagent - 0.121 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
p-methylbenzaldehyde	5.00 g.	0.0417	34.5	98.1
p-methylacetophenone	0.10 g.	0.0007	0.6	1.9

Material distilling over the range 70-108° at 10 mm. pressure, including p-bromotoluene, was collected, and quantities determined from chromatographic data. In addition to the above quantities,

1.8 g. of p-bromotoluene was shown to be present. A sample of the aldehyde was collected at 102-104° at 10 mm. The ketone was present in too small a quantity to be separated.

Formic Acetic Anhydride - m-Chlorophenylmagnesium Bromide: Runs 56-58

Run No. 56

Anhydride - 11.6 g. (0.133 moles). Grignard reagent - 0.133 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
m-chlorobenzaldehyde	2.30 g.	0.0164	12.3	100.0
m-chloroacetophenone	trace			

The unreacted m-chlorobromobenzene from the preparation of the Grignard reagent could not be satisfactorily separated from the aldehyde product by means of either distillation or the Beckman GC-2 chromatograph. The boiling points of the two compounds were too close together, and their retention times were almost the same. The material distilling over the range 80-120° at 20 mm. pressure was analyzed on the Barber-Colman chromatograph, which had just become available. Three compounds were found to be present in sufficient quantity to be determined: a small amount of chlorobenzene (0.55 g., presumably formed from the unreacted Grignard reagent upon hydrolysis), unreacted m-chlorobromobenzene from Grignard reagent preparation (6.55 g.), and the m-chlorobenzaldehyde (2.30 g.). A very small peak was found at the point where m-chloroacetophenone was expected. Since the aldehyde could not be isolated by fractional distillation, aldehyde derivatives were prepared from samples of m-chlorobenzaldehyde contaminated with m-chlorobromobenzene and chlorobenzene.

Formic Acetic Anhydride - Phenylmagnesium Bromide; Tetrahydrofuran Used as Solvent, in Place of Ether: Runs 59-61

Run No. 60

Anhydride - 15.21 g. (0.173 moles). Grignard reagent - 0.173 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
benzaldehyde	4.41 g.	0.0416	24.1	53.9
acetophenone	4.27 g.	0.0355	20.5	46.1

Distillation was carried out as in Run No. 37, described above.

Formic Acetic Anhydride - Ethylmagnesium Bromide: Runs 62-64

Run No. 63

Anhydride - 9.7 g. (0.111 moles). Grignard reagent - 0.111 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
propionaldehyde	trace			
methyl ethyl ketone	trace			
diethyl carbinol	1.22 g.	0.0138	12.4	
methyl diethyl carbinol	1.18 g.	0.0115	10.4	

Chromatographic analysis of the ether solution of the reaction products gave only the relative proportions of the two alcohols. No positive identification of aldehyde or ketone could be obtained. A Schiff's aldehyde test indicated that a trace of aldehyde was present. It was at first thought possible that the aldehyde might have been lost through an aldol condensation, in the presence of the sodium hydroxide wash solution. Therefore, in another run, the ether solution of the reaction products was tested before washing; but again it gave only a trace of aldehyde. As a further test, a known

solution of propionaldehyde and methyl ethyl ketone was subjected to the same conditions as those used for the separation of the products of the Grignard reaction. They were recovered quantitatively; therefore such compounds could not have been lost because of the separation procedure.

No product having a higher boiling point than the tertiary alcohol was indicated on the chromatograph, and there was no tarry residue. Since quantitative yields could not be satisfactorily determined by distillation, they were estimated by assuming that all of the product (after distillation up to the point where diethyl carbinol would be collected) was composed of the two alcohols. This mixture of the two alcohols weighed 2.40 g. A sample of diethyl carbinol was recovered, after combination of the products of this run with those from the other similar runs, at 114-116°.

Formic Acetic Anhydride - Propylmagnesium Bromide: Runs 65-67

Run No. 67

Anhydride - 8.62 g. (0.098 moles). Grignard reagent - 0.098 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
butyraldehyde	0.57 g.	0.0079	8.0	65.0
methyl propyl ketone	0.37 g.	0.0043	4.4	35.0
dipropyl carbinol	0.84 g.	0.0072	7.3	
methyl dipropyl carbinol	1.10 g.	0.0083	8.5	

Chromatographic analysis of the ether solution of products gave the relative proportions of the aldehyde, ketone, and the two

alcohols. The small yield of aldehyde and ketone made the determination of absolute quantities by distillation unsatisfactory. Therefore, a 10 ml. aliquot portion of the 98 ml. ether solution of the reaction products was taken, and the total moles of aldehyde and ketone determined by carbonyl titration. Their absolute quantities were then calculated, using the relative quantities obtained from chromatographic data. An estimation of the absolute quantities of the two alcohols was made, using the relative proportions of the alcohols, aldehyde, and ketone, and the absolute quantities of aldehyde and ketone. The mixed products from all three of these runs were combined, and samples of the individual components were recovered as follows: butyraldehyde, 74-76°; methyl propyl ketone, 100-102°; and dipropyl carbinol, 154-156°.

Formic Acetic Anhydride - Butylmagnesium Bromide: Runs 68-70

Run No. 68

Anhydride - 12.4 g. (0.141 moles). Grignard reagent - 0.141 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
valeraldehyde	3.08 g.	0.0358	25.4	63.4
methyl butyl ketone	2.10 g.	0.0209	14.8	36.6
dibutyl carbinol	1.06 g.	0.0074	5.3	
methyl dibutyl carbinol	2.13 g.	0.0134	9.3	

After chromatographic analysis of the ether solution of reaction products to determine the relative proportions of the four products listed above, the total quantity of aldehyde and ketone was estimated by collecting and weighing the distillate boiling over the range

78-140°. Application of chromatographic data gave the absolute quantities of aldehyde, ketone, and the two alcohols, in a manner similar to that described for Run No. 67, above. The mixed products from all three of these runs were combined, and samples of individual components were recovered as follows: valeraldehyde, 101-103°, methyl butyl ketone, 125-127°; and dibutyl carbinol, 190-194°.

Formic Acetic Anhydride - Butylmagnesium Chloride: Runs 71 and 72

Run No. 72

Anhydride - 11.8 g. (0.135 moles). Grignard reagent - 0.135 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
valeraldehyde	2.72 g.	0.0316	23.4	63.4
methyl butyl ketone	1.82 g.	0.0182	13.5	36.6
dibutyl carbinol	1.73 g.	0.0120	8.9	
methyl dibutyl carbinol	2.96 g.	0.0187	13.8	

A procedure similar to that employed for Run No. 68 was followed in this run.

Formic Acetic Anhydride - Isobutylmagnesium Bromide: Runs 73-76

Run No. 76

Anhydride - 10.6 g. (0.121 moles). Grignard reagent - 0.121 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
isovaleraldehyde	3.71 g.	0.0431	35.6	65.1
methyl isobutyl ketone	2.32 g.	0.0232	19.2	34.9
diisobutyl carbinol	0.35 g.	0.0024	2.0	
methyl diisobutyl carbinol	0.21 g.	0.0013	1.0	

Relative proportions of the four products were determined by chromatographic analysis. Recovery of the total aldehyde and ketone products by distillation was unsatisfactory; therefore the carbonyl titration method was used. The absolute quantities of the reaction products were estimated in a manner similar to that used for previous runs in which alcohols were present as products of the reaction. Samples of the aldehyde and ketone were collected, after combination of the mixed products from all four of these runs, at 90-93° and 116-118°, respectively.

Acetic Butyric Anhydride - Phenylmagnesium Bromide, at 0°: Runs 77-79

Run No. 79

Anhydride - 14.2 g. (0.110 moles). Grignard reagent - 0.110 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Ketones
acetophenone	2.56 g.	0.0213	19.4	43.7
butyrophenone	4.08 g.	0.0275	25.0	56.3
methyl diphenyl carbinol	2.34 g.	0.0118	10.7	
butyl diphenyl carbinol	trace			

Chromatographic analysis of the ether solution of the reaction products gave the relative proportions of acetophenone, butyrophenone, and methyl diphenyl carbinol. Estimation of absolute quantities of the ketones was made by means of distillation at 20 mm. over the range 89-122° to find the total yield, and relative proportions were calculated from the chromatographic data. The quantity of methyl diphenyl carbinol was estimated by using the relative proportions of alcohol and the two ketones, and the absolute quantities of the ketones. A

trace of butyl diphenyl carbinol was also indicated. Attempts at distillation of the methyl diphenyl carbinol at 20 mm. were unsuccessful, as decomposition appeared to take place after 150° was reached. Distillation was therefore stopped; the brown tarry residue weighed 2.76 g. From this, repeated recrystallizations from ethanol and ligroin gave 0.4 g. of a brown substance having a melting point of 56-61°. This was probably the impure tertiary alcohol, but it could not be further purified.

Formic Acetic Anhydride - Phenylmagnesium Bromide, at 0°: Runs 80-82

Run No. 81

Anhydride - 11.5 g. (0.131 moles). Grignard reagent - 0.131 moles.

	Total Yield	Moles	Per cent Yield	Mole Per cent of Total Carbonyl
benzaldehyde	1.30 g.	0.0123	9.4	83.6
acetophenone	0.29 g.	0.0024	1.8	16.4

The carbonyl compounds were determined as described earlier for benzaldehyde and acetophenone (Run No. 37, page 34). No indication of methyl diphenyl carbinol appeared on the chromatogram. Diphenyl carbinol, which was too high boiling to be determined by means of the chromatograph, was shown to be present by means of distillation; this distillation, however, was not sufficiently complete to give a quantitative measure of it. After distillation of the benzaldehyde, acetophenone, and biphenyl (by-product of the preparation of Grignard reagent) from the reaction mixture, the residue weighed 9.8 g. The pressure was reduced to 12 mm.; 3.3 g. of distillate was recovered in the range 156-183°. At approximately

183°, the supply in the distillation flask was exhausted. Throughout the latter part of the distillation, the material in the distillation flask appeared to decompose, giving off a white smoke. The material collected at 156-183° would not crystallize at first, but after about a month's time it had crystallized to give a solid with melting point 66-70°. Recrystallization from ligroin gave a white solid with a melting point of 68-69°, corresponding to that of diphenyl carbinol. Attempts at recrystallization of the remaining brown tarry residue in the distillation flask were unsuccessful, as were attempts made, in other runs, to recover diphenyl carbinol by crystallization without prior distillation.

Table I

Acetic Higher-Carboxylic Anhydrides -- Phenylmagnesium Bromide[a],[b],[c]

Run No.	Anhydride	Per cent Yield of Ketone			Mole Per cent of Ketone	
		Lower MW	Higher MW	Total	Lower MW	Higher MW
1	Acetic butyric	35.3	18.7	54.0	65.4	34.6
2	" "	36.8	19.8	56.6	65.1	34.9
3	" "	35.3	19.2	54.5	64.8	35.2
4	Acetic butyric[d]	39.8	22.4	62.2	64.5	35.5
5	" " [d]	39.1	21.1	60.2	65.1	34.9
6	" " [d]	38.2	19.6	57.8	65.6	34.4
7	Acetic valeric	38.6	21.7	60.3	64.4	35.6
8	" "	41.5	22.3	63.8	65.2	34.8
9	" "	38.6	20.2	58.8	65.8	34.2
10	Acetic caproic	36.9	23.4	60.3	61.6	38.4
11	" "	34.3	22.4	56.7	60.6	39.4
12	" "	36.4	21.5	57.9	63.0	37.0
13	Acetic isobutyric	34.3	14.7	49.0	69.9	30.1
14	" "	35.3	14.7	50.0	70.4	29.6
15	" "	35.2	15.6	50.8	69.3	30.7
16	Acetic α-methylbutyric	49.7	14.3	64.0	77.6	22.4
17	" "	45.4	14.2	59.6	76.1	23.9
18	" "	46.0	13.0	59.0	78.0	22.0
19	Acetic isovaleric	40.0	19.6	59.6	67.0	33.0
20	" "	41.3	21.1	62.4	66.2	33.8
21	" "	40.3	18.6	58.9	68.4	31.6
22	Acetic butyric[e]	45.3	27.9	73.2	62.6	37.4
23	" " [e]	43.9	25.9	69.8	62.9	37.1
24	" " [e]	43.4	26.8	70.2	61.8	38.2
25	Acetic butyric[c]	35.8	27.4	63.2	56.6	44.4
26	" " [c]	34.1	27.1	61.2	55.2	44.8
27	" " [c]	33.9	26.1	60.0	56.6	43.4

(a) All runs in this and following tables were carried out at -78° C., in ether solvent, and using a ratio of 1 mole anhydride to 1 mole Grignard reagent, unless indicated otherwise.

(b) For most of these runs, traces of the lower molecular weight tertiary alcohol were detected on the chromatograph. Calculations of the yields of this by-product, always less than 1%, were inaccurate.

(c) Runs No. 25-27 involved reaction of the anhydride with propylmagnesium bromide, instead of phenylmagnesium bromide.

(d) A ratio of 2 moles anhydride to 1 mole Grignard reagent was used.

(e) Tetrahydrofuran was used as solvent, instead of ether.

Table II

Mixtures of Simple Anhydrides -- Phenylmagnesium Bromide[a],[b]

Run No.	Anhydrides	Per cent Yield of Ketone			Mole Per cent of Ketone	
		Lower MW	Higher MW	Total	Lower MW	Higher MW
1	Acetic butyric	35.3	18.7	54.0	65.4	34.6
2	" "	36.8	19.8	56.6	65.1	34.9
3	" "	35.3	19.2	54.5	64.8	35.2
28	Acetic and Butyric	37.1	21.5	58.6	62.8	37.2
29	" " "	35.4	21.2	56.6	62.7	37.3
30	" " "	36.6	22.4	59.0	62.0	38.0
7	Acetic valeric	38.6	21.7	60.3	64.4	35.6
8	" "	41.5	22.3	63.8	65.2	34.8
9	" "	38.6	20.2	58.8	65.8	34.2
31	Acetic and Valeric	40.2	21.4	61.6	65.5	34.5
32	" " "	39.3	19.9	59.2	66.4	33.6
33	" " "	37.6	20.6	58.2	64.6	35.4

[a] Traces of lower molecular weight tertiary alcohol were also detected in these runs.

[b] Results of the reactions of mixed anhydrides (See Table I) have been included for the benefit of comparison.

Table III

Formic Acetic Anhydride -- Aromatic Grignard Reagents

Run No.	Grignard Reagent	Per cent Yield			Mole Per cent	
		Aldehyde	Ketone	Total	Aldehyde	Ketone
34	PhenylMgBr(a)	31.9	7.1	39.0	82.0	18.0
35	" (a)	35.6	7.7	43.3	82.3	17.7
36	"	37.6	7.9	45.5	83.0	17.0
37	"	35.8	7.4	43.2	82.7	17.3
38	"	36.2	7.9	44.1	82.2	17.8
39	"	33.7	6.5	40.2	83.8	16.2
40	PhenylMgBr(b)	29.8	2.8	32.6	91.4	8.6
41	"	31.4	3.6	35.0	89.6	10.4
42	PhenylMgBr(c)	39.3	6.7	46.0	85.5	14.5
43	" (c)	40.0	6.7	46.7	86.0	14.0
44	" (c)	37.9	7.1	45.0	84.2	15.8
45	o-TolylNgBr	25.4	0.8	26.2	97.0	3.0
46	"	23.6	0.7	24.3	97.0	3.0
47	"	23.2	0.6	23.8	97.2	2.8
48	m-TolylMgBr	34.2	1.0	35.2	97.1	2.9
49	"	31.9	1.1	33.0	96.9	3.1
50	"	33.9	0.9	34.8	97.4	2.6
51	p-TolylMgBr	34.5	0.6	35.1	98.1	1.9
52	"	35.6	0.9	36.5	97.5	2.5
53	"	33.4	0.9	34.3	97.6	2.4
54	p-TolylMgBr(c)	32.5	0.8	33.3	97.6	2.4
55	" (c)	34.7	0.7	35.4	97.9	2.1
56	m-ChlorophenylMgBr	12.3	trace	12.3	100	0
57	"	15.1	"	15.1	100	0
58	"	14.0	"	14.0	100	0
59	PhenylMgBr(d)	23.0	20.2	43.2	53.1	46.9
60	" (d)	24.1	20.5	44.6	53.9	56.1
61	" (d)	24.3	21.1	45.4	53.5	46.5

(a) The anhydride used in Runs No. 34 and 35 was prepared from formic acid and acetic anhydride. All other formic acetic anhydride was prepared from ketene and formic acid.
(b) Large quantities of starting materials were used (approximately 5 times as great as the quantities used in other runs).
(c) A ratio of 2 moles anhydride to 1 mole Grignard reagent was used.
(d) Tetrahydrofuran was used as solvent, rather than ether.

Table IV

Formic Acetic Anhydride -- Aliphatic Grignard Reagents

Run No.	Grignard Reagent	Per cent Yield					Mole Per cent	
		Aldehyde	Ketone	Secondary Alcohol	Tertiary Alcohol	Total	Formic Part	Acetic Part
62	EthylMgBr	trace	trace	13.5	13.1	26.6	51.0	49.0
63	"	"	"	12.4	10.4	22.8	54.6	45.4
64	"	"	"	10.9	9.3	20.2	53.8	46.2
65	PropylMgBr	9.9	5.6	9.0	10.3	34.8	54.3	45.7
66	"	9.2	5.1	8.3	9.1	31.7	55.3	44.7
67	"	8.0	4.4	7.3	8.5	28.2	54.6	45.4
68	ButylMgBr	25.4	14.8	5.3	9.3	54.8	55.8	44.2
69	"	28.2	15.8	3.7	8.9	56.6	56.4	43.6
70	"	26.8	15.7	4.1	9.5	56.1	55.2	44.8
71	ButylMgCl	20.3	12.4	12.5	14.8	60.0	54.7	45.3
72	"	23.4	13.5	8.9	13.8	59.6	54.1	45.9
73	IsobutylMgBr	33.4	18.7	3.6	1.8	57.5	64.5	35.5
74	"	34.7	20.0	2.0	0.9	57.6	63.8	36.2
75	"	32.6	18.7	2.9	1.5	55.7	63.8	36.2
76	"	35.6	19.2	2.0	1.0	57.8	65.0	35.0

Table V

Reactions of Mixed Anhydrides with Phenylmagnesium Bromide at 0° C.

Run No.	Anhydride	Per cent Yield: Carbonyl Products, Lower MW	Carbonyl Products, Higher MW	Lower MW Alcohol	Total	Mole Per cent: Lower MW Part	Higher MW Part
77	Acetic butyric	18.7	25.3	10.1[a]	54.1	53.2	46.8
78	" "	16.9	23.1	11.5[a]	51.5	55.0	45.0
79	" "	19.4	25.0	10.7[a]	55.1	54.6	45.4
80	Formic acetic	5.2	0.8	----[b]	6.0	86.2	13.8
81	" "	9.4	1.8	----[b]	11.2	83.6	16.4
82	" "	6.5	1.4	----[b]	7.9	82.3	17.7

(a) A trace of the higher molecular weight alcohol was detected (see footnote (b), Table I).

(b) The lower molecular weight alcohol was found but could not be determined quantitatively (see the discussion on pages 44-45).

Table VI

Physical Constants of Reaction Products[a]

	Refractive Indices		Boiling Points	
	Reported	Found	Reported	Found
acetophenone	1.5342(20°)	1.5338	92-93°(20 mm)	91-93°
butyrophenone	1.5202(18.25°)	1.5209	114-115°(20 mm)	114-116°
valerophenone	1.5152	1.5149	128-129°(20 mm)	127-129.5°
caprophenone	------	------	135-136°(14 mm)	134-136°
isobutyrophenone	1.5192(16.6°)	1.5202	106-108°(20 mm)	106-108°
∝-methylbutyrophenone	------	------	116-118°(20 mm)	116-118°
isovalerophenone	1.5139(15.3°)	1.5134	119-121°(20 mm)	119-121°
methyl propyl ketone	1.3895(20.2°)	1.3899	102°	100-102°
dipropyl ketone	1.4073(22°)	1.4080	144°	143-144°
methyl butyl ketone	1.3969(17.4°)	1.3975	127°	125-127°
methyl isobutyl ketone	1.396(20°)	1.3967	116.9°	116-118°
benzaldehyde[b]	1.5453(20°)	1.5456	179-180°	179-180°

(a) Physical constants were measured for all products of reaction which could be isolated; however, since physical constants were similar for the same compounds produced in different runs, only a single representative value of each one is listed in the table. Standard sources from which the reported values were taken were references 56, 57, and 58.

(b) Calculated for C_7H_6O: C, 79.24 per cent; H, 5.70 per cent.
Found: C, 79.30 per cent; H, 5.76 per cent.

Table VI (continued)

	Refractive Indices		Boiling Points	
	Reported	Found	Reported	Found
o-methylbenzaldehyde(c)	1.549(19°)	1.5486	94°(10 mm)	92-94°
m-methylbenzaldehyde(d)	1.541(21.4°)	1.5419	93-94°(17 mm)	93-94°
p-methylbenzaldehyde(e)	1.547(16.6°)	1.5454	106°(10 mm)	102-104°
m-chlorobenzaldehyde	-----	------	213-214°	-------
butyraldehyde(f)	1.3843(20°)	1.3840	75°	74-76°
valeraldehyde(g)	1.3945(20°)	1.3946	102.5-103°	101-103°
isovaleraldehyde(h)	1.3902(20°)	1.3904	92.5°	90-93°
diethyl carbinol	1.4077(25°)	1.4085	115.6°	114-116°
dipropyl carbinol	1.4205(20°)	1.4213	155.4°	154-156°
dibutyl carbinol	1.4289(18°)	1.4273	194°	190-194°

(c) Calculated for C_8H_8O: C, 80.00 per cent; H, 6.71 per cent.
Found: C, 80.18 per cent; H, 6.72 per cent.
(d) Calculated for C_8H_8O: C, 80.00 per cent; H, 6.71 per cent.
Found: C, 80.00 per cent; H, 6.57 per cent.
(e) Calculated for C_8H_8O: C, 80.00 per cent; H, 6.71 per cent.
Found: C, 79.91 per cent; H, 6.80 per cent.
(f) Calculated for C_4H_8O: C, 66.63 per cent; H, 11.18 per cent.
Found: C, 66.67 per cent; H, 11.40 per cent.
(g) Calculated for $C_5H_{10}O$: C, 69.72 per cent; H, 11.59 per cent.
Found: C, 69.68 per cent; H, 11.74 per cent.
(h) Calculated for $C_5H_{10}O$: C, 69.72 per cent; H, 11.59 per cent.
Found: C, 69.63 per cent; H, 11.86 per cent.

Table VII

Melting Points of Derivatives of Reaction Products

	Semicarbazone		2,4-Dinitrophenylhydrazone	
	Reported	Found	Reported	Found
acetophenone	203°	202°	250°	248-250°
butyrophenone	188°	187-188°	50°(a)	48-49°
valerophenone	166°	165-166°	123-124°	122-123.5°
caprophenone	132°	130.5-132°	----	----
isobutyrophenone	101°	179-180.5°	94°(a)	93-93.5°
α-methylbutyrophenone	197°	196-197.5°	82°(a)	81-82°
isovalerophenone	210°	208-209.5°	74°(a)	72.5-74°
methyl propyl ketone	110°	110-111°	141°	142-143°
dipropyl ketone	133°	132-133.5°	75°	74.5-75°
methyl butyl ketone	125°	122-123°	106°	105-106°
methyl isobutyl ketone	132°	132-133°	95°	94-95°
benzaldehyde	222°	220.5-222°	237°	235-236.5°
o-methylbenzaldehyde	212°	210.5-211.5°	193°	193-194°
m-methylbenzaldehyde	204°	204-206°	194°	192-193.5°
p-methylbenzaldehyde	234°	232-234.5°	234°	233-234.5°
m-chlorobenzaldehyde	228°	227-228°(d)	216°(b)	214-215.5°
butyraldehyde	77°	75-76.5°	123°	121.5-122°
valeraldehyde	520°(a)	50-52°	106°	106-107°
isovaleraldehyde	107°	105-106°	123°	123-124°
diethyl carbinol	970°(c)	97-98°		
dipropyl carbinol	64°(c)	62-63°		

(a) oxime
(b) p-nitrophenylhydrazone
(c) 3,5-dinitrobenzoate
(d) Calculated for $C_8H_7N_3OCl$: N, 21.24 per cent. Found: 20.96 per cent.

Table VIII

Preparation of Mixed Anhydrides[a]

Run No.	Mixed Acetic Anhydride	Yields (per cent)	Neutralization Equivalent		Per cent Purity	Refractive Index(20^{o})	
			Theory	Found		Reported	Found
2	Acetic butyric	47.5	65.4	66.3	98.4	1.4050	1.4044
7	Acetic valeric	55.0	72.1	72.8	98.9	1.4092	1.4099
10	Acetic caproic	60.9	79.1	80.5	98.4	1.4144	1.4145
13	Acetic isobutyric	58.0	65.4	67.4	97.0	1.3980	1.3972
17	Acetic α-Methylbutyric	48.3	72.1	74.0	97.5	1.4063	1.4070
18	Acetic isovaleric	40.3	72.1	73.8	97.8	1.4054	1.4060
71	Formic acetic[b]	39.4	44.1	44.7	98.5	1.3880	1.3882
34	Formic acetic[c]	13.8	44.1	46.0	95.8	1.3880	1.3824

(a) Since all of each type of anhydride used in Grignard reactions were similar, just one example of each is given. All anhydrides used were indicated by titration to have at least 97.0 per cent purity, with the exception of the formic acetic anhydride prepared by the heating of formic acid with acetic anhydride, followed by distillation.
(b) Prepared by ketene method.
(c) Prepared by the heating of formic acid with acetic anhydride, followed by distillation.

DISCUSSION AND RESULTS

(A) Reactions of Acetic Higher-Carboxylic Anhydrides

The proportions in which the two possible ketones were produced were determined successfully. These results may be found in Table I, page 46. In this discussion, as in the tables, it is to be understood that the Grignard reactions were carried out at -78° C., in ether solution, and with a ratio of one mole anhydride to one mole of Grignard reagent, unless indicated otherwise. The general pattern of behavior of the acetic higher-aliphatic acid anhydrides was as follows:

(a) Acetic straight-chain acid anhydrides: When the anhydrides were allowed to react with phenylmagnesium bromide, the lower molecular weight ketone (acetophenone) always predominated. The proportion of the higher ketone produced was nearly the same for all three anhydrides used, showing, however, a slight and unexplained increase for acetic caproic anhydride. When acetic butyric anhydride was allowed to react with phenylmagnesium bromide in a ratio of 2:1, there was a slight increase in the total yield, based on the quantity of Grignard reagent used, but the proportions of the products remained about the same as they were when equimolar quantities of reactants were used. The reaction of acetic butyric anhydride with

phenylmagnesium bromide in tetrahydrofuran gave a significant increase in the total yield, with a slight increase in the proportion of higher molecular weight ketone. The reaction of acetic butyric anhydride with propylmagnesium bromide gave a total yield higher than that obtained from the reaction with phenylmagnesium bromide, and the predominance of the lower ketone over the higher ketone was decreased significantly.

(b) Acetic branched-chain acid anhydrides with phenylmagnesium bromide: The lower molecular weight ketone was formed in lesser proportions than it was formed in the reactions of the straight-chain anhydrides. The following order of higher ketone formation was found: isovaleric > isobutyric > α-methylbutyric; that is, the isovaleric half of acetic isovaleric anhydride was more effective in ketone formation than was the isobutyric half of acetic isobutyric anhydride, etc. In other words, higher ketone formation decreased as the substituent methyl group was moved from the β-carbon to the α-carbon, and decreased further as the chain length, with the methyl group on the α-carbon, was increased.

The relative proportions of the products in most of these reactions may be explained on the basis of steric hindrance. In all cases, the smaller part of the anhydride has participated in reaction with the Grignard reagent to a greater extent than has the larger part of the anhydride. The extent to which reaction of the larger half of the anhydride with the Grignard reagent took place depended largely upon the steric character of the Grignard reagent used. This is evident upon observation of Table I, page 46, which gives the

results of reactions of acetic higher-carboxylic anhydrides with phenylmagnesium bromide. The effect of branching in the anhydride chain may be seen. Where steric factors of the Grignard reagent have been greatly reduced, by the use of propylmagnesium bromide, in reactions with acetic butyric anhydride, the mole per cents of the lower and higher molecular weight ketones are more nearly the same. Steric factors were also reduced somewhat by the use of tetrahydrofuran as solvent, allowing more of the higher molecular weight ketone to be formed, and giving higher total yields of the two ketones. It was expected that steric hindrance factors would be alleviated by the use of tetrahydrofuran as solvent, rather than ether. Since the Grignard reagent actually exists as a solvated complex, the ethyl groups of ether are more likely to interfere with the reaction of the Grignard reagent than are the groups connected to the oxygen of tetrahydrofuran, which are "tied together" and held away from the point of reaction.

The results of the reactions of the mixtures of simple anhydrides with phenylmagnesium bromide did not differ significantly from the results of the reactions of the corresponding mixed anhydrides. These reactions have been compared in Table II, page 47. These results were in marked contrast to the previous work of this sort in the Friedel-Crafts reaction, described on pages 13 and 14, with the same simple and mixed anhydrides, and with the work of the present author using benzoic p-nitrobenzoic anhydride and the corresponding simple anhydrides. In those Friedel-Crafts studies,

mixed anhydrides were found to give molar ratios of products which differed substantially from the ratios obtained with mixtures of simple anhydrides.

When the reaction of acetic butyric anhydride with phenylmagnesium bromide was carried out at 0° C., the results found in Table V, page 50, were obtained. A considerable quantity of the lower molecular weight tertiary alcohol was formed. Taking this alcohol into consideration, the total yield was not significantly different from the yield of the same reaction at -78° C. However, the ratio of reaction of the acetic part of the anhydride to reaction of the butyric part was smaller than the corresponding ratio when the reaction was carried out at -78° C.

(B) Reaction of Formic Acetic Anhydride

In all of the reactions of formic acetic anhydride, with the exception of those with m-chlorophenylmagnesium bromide, and ethylmagnesium bromide, both the aldehyde and the ketone products possible were indicated by the chromatograph to be present, and both were estimated quantitatively using chromatographic data. All of these carbonyl compounds were identified positively, with the exception of the ketones produced by the reactions of formic acetic anhydride with o-, m-, and p-tolylmagnesium bromides. The ketone, indicated qualitatively by the chromatograph in each of these runs, was present in too small a quantity to be separated and identified positively. In the reactions of formic acetic anhydride with aliphatic Grignard reagents, alcohols were produced, as a result of

further reaction of the Grignard reagents. The relative and absolute quantities of these secondary reaction products were determined, in addition to the quantities of the aldehydes and ketones.

The results of the reactions of formic acetic anhydride with aromatic Grignard reagents may be found in Table III, page 48. There was no apparent difference in the reactions, with phenylmagnesium bromide, of the anhydride prepared by the ketene method and that prepared from formic acid and acetic anhydride, although the per cent purity of the latter, as calculated from neutralization equivalents, was lower. When a ratio of 2 moles anhydride to 1 mole Grignard reagent was used, the total yield, and the proportion of aldehyde to ketone, was very slightly increased. When tetrahydrofuran was used as solvent, the ratio of aldehyde to ketone was very greatly decreased, the proportions becoming nearly equal. Upon the use of Grignard reagents having a methyl group on the ring, instead of phenylmagnesium bromide, the proportion of aldehyde in the product was increased. There was little difference in the aldehyde--ketone ratios obtained from o-, m-, and p-tolylmagnesium bromides. The total yields of carbonyl compounds were decreased, as compared to the total yields when phenylmagnesium bromide was used. The yields were about the same for the reactions of m- and p-tolylmagnesium bromide, but the yield was less for the reaction of o-tolylmagnesium bromide with the anhydride. Reaction of m-chlorophenylmagnesium bromide with the anhydride gave only a trace of ketone, and the yield of aldehyde was lowered considerably, as compared to the yields from the reactions of the other aromatic Grignard reagents.

In Runs No. 40 and 41, large quantities of phenylmagnesium bromide and formic acetic anhydride were used (about 5 times as great as the quantities used in previous runs). These larger-scale reactions were carried out in order to explore the feasibility of obtaining a reasonably pure aldehyde, by this method, in fairly substantial quantity. Run No. 40 has been described in detail on pages 35-36. Runs No. 40 and 41 showed a decrease in the total per cent yields of the carbonyl products, particularly a decrease in the ketone yield, as compared to similar runs involving smaller quantities of starting material. The predominance of aldehyde over ketone was greater than in the previous similar runs. One possible explanation of these differences is the longer time of reaction in Runs No. 40 and 41; the Grignard reagent was added over a period of 2-1/2 hours, followed by 2 hours of further reaction, as opposed to 3 hours total reaction time for the previous runs. Another explanation is the possibility that the larger quantities of reacting materials made cooling of the reaction vessel inadequate, causing the lower total yields and the change in the ratio of products.

The general pattern of behavior of formic acetic anhydride in reactions with aliphatic Grignard reagents (Table IV, page 49), seemed to be the following:

(a) Aliphatic magnesium bromides: Secondary and tertiary alcohols were considered, in addition to the aldehydes and ketones. Both the total yields, considering all products, and the total yields of carbonyl products, decreased in the following order of Grignard reagents: isobutyl- > butyl- > propyl- > ethylmagnesium bromide.

The yields of alcoholic secondary reaction products increased in this same order; the reaction of formic acetic anhydride with ethylmagnesium bromide gave the most alcohol. However, the molar ratio of products from reaction of the formic part of the anhydride to products from the acetic part remained about the same when the unbranched Grignard reagents were used; that is, ethyl-, propyl-, and butylmagnesium bromides. This ratio was increased when isobutylmagnesium bromide was used.

(b) Butylmagnesium chloride: Somewhat more of the secondary reaction took place, lowering the yields of aldehyde and ketone and giving larger yields of alcohol. However, the molar ratio of products from the formic part to the acetic part of the anhydride remained about the same as that for butylmagnesium bromide and the other straight-chain Grignard reagents.

The results of the reactions of formic acetic anhydride with Grignard reagents, like the reactions of higher mixed acetic anhydrides, may be explained on the basis of steric factors. These factors become evident upon observation of the results of reactions of formic acetic anhydride with aliphatic Grignard reagents. The reaction of the formic part of the anhydride took place to only a slightly greater extent than did the acetic part, when straight chain Grignard reagents were used. When reactions of the anhydride with straight chain Grignard reagents are compared to the reaction with isobutylmagnesium bromide, the differences are evident. Not so readily explainable, however, are the low yields of aldehydes and ketones and the low total yields from the reactions of formic

acetic anhydride with ethylmagnesium bromide and propylmagnesium bromide. It would be expected, from the work of Newman and co-workers, that the complex formed at -78° C. would prevent further reaction to give the alcohols. But even if the secondary reaction did take place, larger yields of the alcohols would be expected. The most likely explanation is that the anhydride remained partially unreacted.

The relative proportions of the aldehyde and ketone formed by the reaction of formic acetic anhydride with phenylmagnesium bromide may also be explained by means of steric factors. The formic part of the anhydride can react much more readily with the Grignard reagent. When the same reaction was allowed to take place in tetrahydrofuran, in which it was expected that any steric hindrance factors would be diminished, as explained on page 57, the ratio of aldehyde to ketone was greatly decreased. In fact, it approached the ratio of products from the formic part of the anhydride to products from the acetic part that was found for the reaction of formic acetic anhydride with straight-chain aliphatic Grignard reagents.

It was expected that the total yields from the reactions of p- and m-tolylmagnesium bromides with formic acetic anhydride would be at least as great as the yields from the reaction of phenylmagnesium bromide. In fact, it seems that the electron-releasing ability of the methyl group would permit the Grignard reagent to react more readily with the electrophilic carbon of the carbonyl group of the anhydride. However, as described on page 59, yields from these reactions were lower than yields from the reaction of

phenylmagnesium bromide, and the proportions of ketones present in the reaction products were very small. These results could not be explained; it is unlikely that the presence of a methyl group in the para or meta position would provide enough steric hindrance to explain the low yields. o-Tolylmagnesium bromide acted as would be expected from a consideration of steric factors, giving a lower yield of aldehyde and ketone; however, the relative proportions of the aldehyde and ketone remained about the same as proportions from the reactions of the meta and para substituted Grignard reagents.

The reduced yields of both products, and particularly of the ketone, when m-chlorophenylmagnesium bromide reacted with formic acetic anhydride, might be ascribed to electronic effects. Since the chlorine and methyl are about the same size, little difference in the reactions of the corresponding chloro and methyl substituted reagents would be expected on the basis of steric effects. The electron-withdrawing chlorine may have decreased the chance of reaction at the electrophilic carbon of the anhydride carbonyl group.

When the reaction of formic acetic anhydride with phenylmagnesium bromide was carried out at 0° C. (Table V, page 50), the yields of carbonyl products were greatly decreased from the yields of the corresponding reaction at -78° C. The molar ratio of aldehyde to ketone remained about the same as that for the low temperature reaction, but these figures were probably insignificant due to the inability of the author to recover quantitatively the secondary reaction products.

The present work has been notable, in that aldehydes were prepared from the reactions of formic acetic anhydride with Grignard reagents. It developed that the main interest of the present work lay in this aldehyde synthesis, a method which has not been reported previously in the literature. In all cases, the aldehyde predominated over the ketone product, and in some cases the aldehyde was formed exclusively. As discussed on page 8, previous attempts to obtain aldehydes from formic acetic anhydride, from the Friedel-Crafts reaction of the anhydride with benzene and other aromatics, were unsuccessful. Perhaps the formic part of the anhydride was destroyed in the presence of the aluminum chloride catalyst.

As a practical method of preparation, there are a number of shortcomings in this new synthesis which must be recognized. Yields of aldehydes ranged from 8 to 40 per cent. There are some inconveniences in the preparation and use of formic acetic anhydride, particularly in large scale operations. It was difficult to prepare a large quantity of the anhydride, using the methods available. The cooling of its reaction with the Grignard reagent, in order to maintain the very low temperature, was difficult; it was necessary to add the Grignard reagent slowly, over a long period of time. The anhydride was always used soon after its preparation, due to its supposed instability; however, no tests have been carried out for the purpose of determining how long a period of time a batch of this anhydride would retain its usefulness for aldehyde preparation. A limitation of this reaction is the impossibility of using materials

incompatible with Grignard reagents, such as compounds containing hydroxy or nitro groups. There is need for much further study of variations of reagents, and of conditions, which might give various other aldehyde products, or higher yields, or both.

(C) Further Discussion of Controlling Influences

The phenomenon of steric hindrance has also been used to account for the ratios of products observed in the reactions of unsymmetrically substituted phthalic anhydrides with Grignard reagents. Some of the work of Newman and co-workers on the reactions of 3-methylphthalic anhydride and 3-chlorophthalic anhydride with Grignard reagents has been tabulated in the following manner (36):

Grignard reagent	3-Methylphthalic anhydride Per cent reaction		3-Chlorophthalic anhydride Per cent reaction	
	1 carbonyl	2 carbonyl	1 carbonyl	2 carbonyl
PhenylMgBr	43	14	52	12
m-XylylMgBr	39	4	66	17
MesitylMgBr	66	1	49	0

Sizeable quantities of unreacted anhydride were recovered in most cases. The work with 3-chlorophthalic anhydride was undertaken by Newman and Scheurer (36), to see what effect the substitution of a chlorine atom for a methyl group on the anhydride might have, the work with 3-methylphthalic anhydride having been done previously (32,33). Since chlorine and methyl are about the same size, deviations from the trend for methyl would be evidence that the polar effect of the chlorine atom had a predominant influence on the reactivity of the carbonyl functions and on the course of reaction.

As may be seen from the listed results, reaction of 3-chlorophthalic anhydride with both phenylmagnesium bromide and m-xylylmagnesium bromide took place at the 1-carbonyl and 2-carbonyl functions in the ratio of about 4:1. Reaction of mesitylmagnesium bromide took place exclusively at the 1-carbonyl function. These results were similar to the results of the reactions of 3-methylphthalic anhydride with these same Grignard reagents. Scheurer (43) concluded in general that the usual type of steric hindrance accounted for the ratio of the products observed in the Grignard reaction.

In addition to their study of the reactions of 3-chlorophthalic and 3-methylphthalic anhydrides with Grignard reagents, Newman and Scheurer carried out a study of these two anhydrides in the Friedel-Crafts reaction. When 3-chlorophthalic anhydride was allowed to react with benzene, and m-xylene, reaction took place exclusively at the hindered, or 2-carbonyl function. Only when mesitylene was used did some reaction occur at the unhindered carbonyl function. Results of reactions of 3-methylphthalic anhydride with the same aromatic reagents also varied widely from results of the corresponding Grignard reactions, although the contrast was not so extreme as in the case of 3-chlorophthalic anhydride. Comparisons of these reactions indicate the importance of steric factors in the Grignard reactions of unsymmetrically substituted cyclic anhydrides, as compared to steric hindrance in the Friedel-Crafts reaction.

Farrugia, Sibille, and the present author, in work with mixed anhydrides in the Friedel-Crafts reaction, have concluded that, in the Friedel-Crafts reaction, a combination of electronic and steric

effects must be considered in the determination of the relative reactivities of the two acyl groups of a mixed anhydride. Results of the present work make it seem apparent that, in the Grignard reaction, the dominating factor in the determination of the relative reactivities of the acyl groups of the anhydride is the steric character of those radicals.

(D) Validity of Experimental Results

In any work with mixed carboxylic anhydrides, there is an unavoidable degree of error, the extent of which is sometimes hard to determine. This results from the disproportionation tendency of these reagents, and from the lack of absolute methods of determining the precise extent of that disproportionation. It is appropriate, therefore, to review the reasons for believing that those anhydrides used in the present work were sufficiently pure to give significance to the results obtained with them in the Grignard reactions. An example of each anhydride used may be found in Table VIII, page 54. The neutralization constants closely approached the theoretical values, indicating that impurities other than those due to disproportionation were slight. Refractive indices checked with those measured by previous workers, including Sibille (44), who used the same anhydrides, with the exception of formic acetic anhydride, in Friedel-Crafts acylation of benzene. Elemental analyses of Sibille's anhydrides showed that their elemental content approached the theoretical values. Elemental analysis of formic acetic anhydride, used in the present work, was not secured; the reason was given in

Experimental Part. The only impurities likely to be present in the anhydrides were those due to disproportionation occurring during the brief interval between the final carbonate washing or distillation, and use in the Grignard reaction, since any unreacted acid or simple anhydride present was removed by this carbonate washing, or by distillation. Anhydrides were used as soon as possible after drying or distillation, in order to minimize disproportionation.

SUMMARY

A study has been made of the low temperature reactions of mixed carboxylic anhydrides with Grignard reagents. A total of seven anhydrides were used; including formic acetic anhydride, which received major attention, and six higher mixed acetic anhydrides. A variety of Grignard reagents were allowed to react with these anhydrides, usually in ether, but sometimes using tetrahydrofuran as solvent. Reactions of the higher mixed acetic anhydrides were carried out mainly with phenylmagnesium bromide. In addition, a study was made of the reactions of mixtures of acetic and butyric anhydrides, and acetic and valeric anhydrides, with phenylmagnesium bromide.

The relative proportions of the two possible carbonyl products were determined. In addition, in some reactions, the proportions of alcohols formed as secondary reaction products were determined. Attempts have been made to correlate the relative reactivities of the acyl groups of the anhydrides with the structures of those acyl groups and of the Grignard reagents used.

The reactions of formic acetic anhydride with Grignard reagents yielded, predominantly, aldehydes. This was a new method of aldehyde synthesis, giving yields of aldehydes ranging from 8 to 40 per cent.

Both aromatic and aliphatic aldehydes were formed by use of five aromatic, and four aliphatic Grignard reagents. Here, also, attempts have been made to correlate the total and the relative amounts of aldehydes and ketones with the structural details of the Grignard reagents. Initial steps have been taken in a study of the influences of temperature, solvent, etc., on the yields of aldehydes.

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VITA

Karl P. Kammann, Jr. was born in St. Louis, Missouri on March 30, 1936, the son of Mr. and Mrs. Karl P. Kammann. He received his primary and secondary education from public schools in St. Clair County, Illinois; Signal Hill School and Belleville Township High School. He was graduated from the latter in June, 1953, and in September of that year entered Washington University, St. Louis, Missouri. In June, 1957, he received the Bachelor of Arts degree from Washington University. He entered the Graduate School of Louisiana State University in February, 1958, and worked under the direction of Professor W. R. Edwards, Jr. until he received the Master of Science degree in chemistry in June, 1960.

He was married to the former Carmelita Sue Pranter of University City, Missouri, on June 17, 1960. They now have a daughter, Caroline Susan. In September of 1960 he again entered the Graduate School of Louisiana State University, where he served as a teaching assistant for the year 1960-61. He was given a University Research Assistantship for the year 1961-1962, and is now a candidate for the degree of Doctor of Philosophy.

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Major Field: Chemistry

Title of Thesis: Mixed Carboxylic Anhydrides in the Grignard Reaction

Approved:

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